Attorney Docket No. 1909.03 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Wettstein et al.	)	
	)	
Application No.: 10/099,924	)	
	)	Group Art Unit: 1643
Filed: March 14, 2002	)	
	)	Examiner: A. Harris, Ph.D.
For: SURVIVIN-INTERACTING PROTEINS AND USE THEREOF	)	
	)	

RESPONSE TO NOTIFICATION OF NON-COMPLIANT APPEAL BRIEF (37 C.F.R. § 41.37)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with MPEP § 1205, an Amended Appeal Brief is transmitted/filed herewith in response to the Notification of Non-Compliant Appeal Brief mailed September 26, 2006, the one-month period for response to which expires on October 26, 2006.

In the Notification, the Appeal Brief filed June 1, 2006 is deemed defective for failing to comply with 37 C.F.R. §§ 41.37(c)(1)(viii) and 41.37(c)(1)(x). Specifically, the Notification alleges that the Brief as filed (1) does not contain a "Related Proceedings Appendix" and (2) contains a "Claims Appendix" that includes claims other than those involved in the appeal.

Appellants have amended the Appeal brief of June 1, 2006 to include the missing Related Proceedings Appendix and to correct the Claims Appendix. The Amended Brief differs from the Appeal Brief filed June 1, 2006 **only** in that (1) a "Related Proceeding Appendix" has been inserted on page 23; and (2) the "Claims Appendix," beginning on

page 19, has been amended to remove all claims not currently on appeal. The Amended Brief is now in compliance with 37 C.F.R. § 41.37(c)(1).

CONCLUSION

The Amended Brief is believed to be in compliance with the requirements of 37 C.F.R. § 41.37(c)(1). Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact Applicants' undersigned attorney.

It is not believed that any time extension or fees are required with this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency or credit any over payment to Deposit Account no. **50-1627**.

Respectfully submitted,

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Date: October 3, 2006

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Filed: March 14, 2002	Group Art Unit: 1643
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AMENDED APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants submit this Amended Appeal Brief in response to the Notification of Non-Compliant Appeal Brief mailed September 26, 2006.

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(1) REAL PARTY IN INTEREST

The real party in interest is Myriad Genetics, Inc., a corporation of the State of Delaware, having a place of business at 320 Wakara Way, Salt Lake City, Utah 84108, to whom all interest in the present Application has been assigned by virtue of an Assignment recorded on May 26, 2002, (at reel 012935, and frame 0078).

(2) RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences that will directly affect, or be directly affected by, or have a bearing on, the Board of Patent Appeals and Interferences' decision in the present appeal.

(3) STATUS OF CLAIMS

Claims 11-26, 40-50 are currently pending in the Application. Claims 11-26 have been withdrawn from consideration. Claims 40-50 were finally rejected in a Final Office Action mailed on September 1, 2005, and are being appealed. Of these eleven appealed claims, only two (40 and 45) are independent claims.

(4) STATUS OF AMENDMENTS

A final rejection was issued and mailed in this case on September 1, 2005. According to this final rejection, the Amendments dated April 4, 2005 and May 5, 2005 were entered into the record. The present appeal is based on the listing of claims presented in the May 5, 2005 Amendment, and reproduced in the attached Claims Appendix.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention generally relates to the inventor's discovery that two human proteins well known in the art, survivin and HDLC1, interact with each other and form a protein complex. The interaction and the protein complex can be used for drug screening to identify drug candidates.

The rejected claims are generally drawn to isolated protein complexes formed based on the protein-protein interaction between survivin and HDLC1. Specifically, the

claims encompass isolated protein complexes between (a) full-length human survivin and HDLC1, (b) fragments of these proteins that retain the ability to interact, (c) homologous proteins that have amino acid sequences with varying degrees of identity to the human proteins and that retain the ability to interact, and (d) fusion proteins comprising the aforementioned interacting polypeptides.

Independent Claim 40 reads upon an isolated protein complex comprising a first protein interacting with a second protein. In claim 40, "said first protein" is (a) full-length survivin or a fragment thereof that interacts with HDLC1, (b) homologues of survivin having an amino acid sequence at least 80% identical to survivin, or fragments thereof, and that are capable of interacting with HDLC1, or (c) a fusion protein comprising (a) or (b). In claim 40, the second protein is selected from the group of (i) full-length HDLC1 or a fragment thereof that interacts with survivin, (ii) homologues of HDLC1 having an amino acid sequence at least 80% identical to HDLC1, or fragments thereof, and that are capable of interacting with survivin, and (iii) fusion proteins containing (i) or (ii).

Independent Claim 45 reads upon an isolated protein complex comprising a first protein interacting with a second protein. In claim 45, "said first protein" is chosen from (a) full-length survivin protein, (b) a survivin protein fragment that contains a contiguous span of at least ten amino acids residues of survivin and that interacts with HDLC1, and (c) homologues of survivin having an amino acid sequence at least 90% identical to survivin, or fragments thereof, and that are capable of interacting with HDLC1. In claim 45, the second protein is (i) full-length HDLC1, (ii) a fragment thereof that contains a contiguous span of at least ten amino acids residues of HDLC1 and that interacts with survivin, or (iii) homologues of HDLC1 having an amino acid sequence at least 90% identical to HDLC1, or fragments thereof, and that are capable of interacting with survivin.

Support for the various elements of Claims 40 and 45 can be found throughout the specification. For example, the specification refers to full-length, native survivin involved in a complex with HDLC1 at p. 27, lines 30-31. Peptides "at least 80% identical" and "at least 90% identical" are discussed at p. 17, lines 11-14; p. 27, line 30 to p. 28, line 12; p. 96, lines 23-25; and p. 97, lines 2-16. Support for survivin and HDLC1 fragments having "a

contiguous span of 10 amino acids" can be found at p. 96, line 28 to p. 97, line 2; p. 97, lines 7-16, and p. 27, line 30 to p. 28, line 12. Specifically, the specification at p. 27, line 30 to p. 28, line 12 discloses that the protein complex of the invention can be formed using survivin fragments capable of interacting with one of the survivin interactors such as HDLC1, and/or a fragment of a survivin interactor (e.g., HDLC1) capable of interacting with survivin. The specification further provides that such protein fragments can include polypeptides having a contiguous span of 10 amino acids or more of the sequence of survivin or an interactor thereof. See specification, p. 96, line 28 to p. 97, line 2; p. 97, lines 7-16. Finally, fusion proteins comprising survivin and HDLC1 fragments are discussed in Table 1, p. 21 (which outlines the results of the yeast two-hybrid experiments detailed on p. 118, line 20 through p. 119, line 24).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 40-50 are unpatentable under 35 USC § 112, first paragraph, as representing new matter not supported in the specification.
2. Whether claims 40-50 are unpatentable under 35 USC § 112, first paragraph, as being based on a disclosure with insufficient written description.
3. Whether claims 40-50 are unpatentable under 35 USC § 112, first paragraph as being based on a nonenabling disclosure.

(7) ARGUMENT

As is clear from the Grounds of Rejection section above, the pending claims stand finally rejected as representing new matter, as being based upon a disclosure that allegedly provides insufficient written description, and as being based upon an allegedly nonenabling disclosure. These rejections, as applied in the Final Office Action, and Appellants' responses to these rejections are now presented.

A. Rejection under 35 USC § 112, first paragraph – New Matter

Claims 40-50 stand finally rejected under 35 USC § 112, first paragraph, as being allegedly directed to new matter not supported in the as filed specification. Under § 112,

first paragraph, the specification must provide a written description of the invention. This requirement, in conjunction with § 132, has been interpreted to prohibit amendments to claims that add new subject matter not sufficiently described in the as filed specification. See generally, MPEP § 2163.06, 8th Edition, Rev. 3, Aug. 2005, p. 2100-190. To avoid such a "new matter" rejection, applicants amending claims are encouraged to include with their amendment citations to the as filed specification pointing out specific support for any changes in the claimed subject matter. MPEP § 2163.06, 8th Edition, Rev. 3, Aug. 2005, p. 2100-190. Examiner thus required that Appellants point to specific portions of the specification that support the claims added in the Amendments of April 4 and May 5, 2005.

Appellants responded to Examiner's Final Rejection in an Amendment dated November 1, 2005. In this Amendment, Appellants pointed to numerous tracts of the specification that supported the objected to portions of Claims 40-50. The relevant portion of the Amendment dated November 1, 2005 has been reproduced here:

> The specification refers to peptides "at least 80% identical" and "at least 90% identical" at p. 17, lines 11-14; p. 27, line 30 to p. 28, line 12; p. 96, lines 23-25; and p. 97, lines 2-16. Support for survivin and HDLC1 fragments having "a contiguous span of 10 amino acids" can be found at p. 96, line 28 to p. 97, line 2; p. 97, lines 7-16, and p. 27, line 30 to p. 28, line 12. Specifically, the specification at p. 27, line 30 to p. 28, line 12 discloses that the protein complex of the invention can be formed using survivin fragments capable of interacting with one of the survivin interactors such as HDLC1, and/or a fragment of a survivin interactor (e.g., HDLC1) capable of interacting with survivin. The specification further provides that such protein fragments can include polypeptides having a contiguous span of 10 amino acids or more of the sequence of survivin or an interactor thereof. See specification, p. 96, line 28 to p. 97, line 2; p. 97, lines 7-16.

As is clear from the above, the claims are not directed to new matter and are fully supported by the as filed specification. Appellants therefore submit that this ground for rejection has been obviated and that this new matter rejection should be reversed.

B. Rejection under 35 USC § 112, first paragraph – Written Description

Claims 40-50 are finally rejected under 35 USC § 112, first paragraph as being based upon a disclosure that allegedly lacks sufficient written description of the invention. In order to satisfy its burden of proving a lack of written description, an

examiner must present prima facie evidence that one skilled in the art could not reasonably conclude that the applicant had possession of the invention at the time of filing. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see also In re Wertheim, 541 F.2d 257 (CCPA 1976). Appellants submit that in the present case the Examiner, through conclusory allegations unsupported by the evidence, fails to establish a prima facie case of insufficient written description.

The Federal Circuit, in the recent case of Invitrogen v. Clontech, has found a genus of proteins sufficiently described by only one disclosed species. Invitrogen, 429 F.3d 1052 (Fed. Cir. 2005). At issue in Invitrogen was a claim directed to

> [a]n isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

Id. at 1072. The court held that limitation of the claimed genus in terms of structure (isolated polypeptide) and function (having DNA polymerase activity and substantially reduced RNase H activity) was sufficient to satisfy the written description requirement. Id. at 1073-4. Because the reverse transcriptase proteins were well known in the art, a single representative embodiment, paired with test data showing that an enzyme produced by the listed sequence indeed had the claimed functional activity, was sufficient to describe the full range of the claimed genus of proteins. Id. at 1073.

The position of the Examiner is that Appellants' disclosure of three specific interactions between survivin and HDLC1 fragments is not sufficient written description of the full genus of polypeptides and fragments that would be encompassed by the claims. Examiner nominally states that "Applicants are not required to disclose every species encompassed by a genus," Final Rejection, p. 7, 3rd paragraph, but contradictorily states that Appellants must describe and provide data for "any and all homologues, derivatives or fragments of the first and second proteins within an isolated protein complex or fusion protein," Final Rejection, p. 7, 1st paragraph. Examiner supports this position by quoting selected portions of the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, 'Written Description' Requirement." Final

Rejection, pp. 8-9 (quoting 1242 Official Gazette 174 for the proposition that a genus must be described by a "representative number of species;" also available at 66 F.R. 1099).

Examiner has failed to establish prima facie lack of written description because Examiner's contentions are at odds with Federal Circuit case law and the instructions found in the PTO's own written description guidelines.

1. Federal Circuit Case Law

Appellants submit that the Federal Circuit's analysis in Invitrogen is particularly suited to the claims presently at issue. Like the claims in Invitrogen, Appellants' claims are also defined by polypeptides (survivin, HDLC1 and fragments and specific homologs thereof) with specific functional limitations (capability of specific protein interactions). The instant Specification clearly provides support for such claims by describing (1) structure in the form of the amino acid sequence of representative embodiments of the claimed interacting proteins and fragments thereof; and (2) function in the form of a specific interaction between the first and second protein or fragments thereof. See Specification, p. 21, Table 1. Both survivin and HDLC1 were well known human proteins in the art at the time of filing. See generally, Specification, p. 22-25 (discussing biological roles of survivin and HDLC1 as elucidated through abundant art research). The nucleotide and amino acid sequences of both proteins were also known in the art by the filing date of this application, as evidenced by the accession numbers associated with each. Specification, p. 21, Table 1. In addition, various methods for determining the claimed feature (ability to interact) in survivin, HDLC1 and fragments, and homologs thereof are also provided in the specification, including detailed discussions of the yeast two-hybrid system. Specification, p. 42-44; see also, id. at p. 57-68.

Thus, like the patents in Invitrogen, the present specification describes at least one (indeed three actual examples) embodiment of the invention that possesses both the functional and the structural elements enumerated in the claims. Examiner has failed to show any reason why the present case is different from that of Invitrogen and thus has failed to provide prima facie evidence of insufficiency of the written description. In fact, the instant Specification is a fortiori sufficient because three distinct examples of protein

complexes were formed and tested rather than the one in Invitrogen. Specification, p. 21, Table 1. Clearly, under the Invitrogen analysis the specification is sufficient to meet the written description requirement.

Another relevant case is Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005). In Capon, the court was faced with claims to chimeric genes that had been rejected by the Board of Patent Appeals as lacking a sufficient written description. The Board cited as ground for its rejection the fact that the specification relied heavily on references "to contemporary and/or prior knowledge in the art of the structure, formula, chemical name, or physical properties of many protein domains, and/or DNA sequences…" Id. at 1355. Further, the Board alleged that an artisan would have to rely on additional knowledge in the art and perform additional experimentation and tests in order to visualize and recognize the identity of the claimed invention. Id. The court rejected this reasoning, specifically holding improper the Board's refusal to "consider the state of the scientific knowledge" as referenced in the applicants' specifications. Id. at 1357.

The instant disclosure is sufficient because Appellants have given more than the description required under Capon. The Capon court found fragments of known genes to be sufficiently described. Id. at 1352 (giving language of claim 1, which was directed to a "gene segment"). That the claims were directed in part to gene fragments was not fatal to the written description because the underlying full-length genes were well known in the art. In the present case, Examiner's rejection based on the claiming of fragments of proteins is similarly improper because the underlying full-length proteins are well known in the art and the disclosure provides a specific description of representative fragments. See Specification, p. 21, Table 1.

As current case law indicates that anyone skilled in the art would readily recognize that Appellants were in possession of the full scope of their claimed invention at the time of filing, Appellants respectfully traverse Examiner's rejection under § 112, first paragraph – written description.

2. USPTO Guidelines

The United States Patent and Trademark Office (PTO) has issued guidelines for the examination of patent applications under the 35 USC § 112, first paragraph, written

description requirement. Though these guidelines do not have the force of law, MPEP § 2163, 8th Edition, Rev. 3, Aug. 2005, p. 2100-171 – 2100-172, a detailed discussion of their application to the present appeal is warranted since the Federal Circuit has explicitly incorporated them into its jurisprudence. See Invitrogen Corp. v. Clontech Laboratories, Inc., 429 F.3d 1052, 1072 (Fed. Cir. 2005); Enzo Biochem Inc. v. Gen-Probe, Inc. 323 F.3d 956, 964 (Fed. Cir. 2005); University of Rochester v. G.D. Searle, 358 F.3d 916, 925 (Fed. Cir.2004). The PTO' guidelines state generally that the written description requirement of 35 USC § 112, first paragraph, can be met by

> show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics … i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Guidelines for Examination of Patent Applications under 35 USC § 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001) (emphasis added) (hereinafter "the Guidelines"). In the particular domain of genus claims, the written description requirement will be fulfilled by disclosure of "relevant, identifying characteristics" such as, again, "functional characteristics coupled with a known or disclosed correlation between function and structure." Id. The Guidelines state, "'representative number of species' means that the species which are adequately described are representative of the entire genus," not that every species encompassed by the claims must be individually supported. Id. (citing In re Bell, 991 F.2d 781, 785 (Fed. Cir. 1993); In re Baird, 16 F.3d 380, 382 (Fed. Cir. 1994)). In some cases a "variety of species" will be required while in others "one species adequately supports a genus." Id. Thus, under the Guidelines, an examiner rejecting claims for lack of written description must provide prima facie evidence that the applicant has not disclosed functional characteristics coupled with a known or disclosed correlation between function and structure. Examiner has failed to do so in the present case.

By citing out of context a single phrase from the Guidelines, Examiner alleges that "representative number of species" necessarily means several or at least more than three species. Such a reading is inconsistent with the portions of the Guidelines cited above. Describing only one species may be sufficient under the Guidelines. See

Guidelines, 66 Fed. Reg. at 1106. Indeed, the key factual inquiry is "whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus in view of the species disclosed." Id. Examiner points to no common attributes that might be missing from the disclosure and instead makes the conclusory statement that "[a]pplicants are not in possession of unidentified and uncharacterized homologues, derivatives and fragments" of the claimed proteins. Final Rejection, p. 8, 2nd paragraph.

On the contrary, such "necessary common attributes" permeate the entire application. For instance, Claim 40 is directed to polypeptides that are either identical or structurally similar to survivin to at least a minimum degree (80%). Thus all members of the genus must meet these strict structural requirements. Besides, survivin polypeptides encompassed by Claim 40 must also bind HDLC1. Methods of determining the binding between survivin or a homologue, or fragment thereof and HDLC1 or a homologue, or fragment thereof are specifically provided thoughout the specification. Since the genus is thus limited in terms of both structure and function, anyone skilled in the art would recognize that Appellants were in possession of the "necessary common attributes" of the claimed genus. Examiner alleges "structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure." Final Rejection, p. 8, 2nd paragraph. Appellants find this statement inexplicable in light of the stringent structural requirements laid out in claims such as Claim 40. See also, Specification, p. 17, lines 11-14; p. 27, line 30 to p. 28, line 12; p. 96, lines 23-25; and p. 97, lines 2-16.

Though not binding law, similarly instructive is Example 14 of the PTO's Revised Interim Written Description Guidelines Training Materials (hereinafter "Training Materials"). USPTO Revised Interim Written Description Guidelines Training Materials, p. 53. In this example a claim to a polypeptide supported by only one disclosed embodiment is held out as allowable. The hypothetical claim of Example 14 defines the protein genus in terms of percent sequence identity and catalytic function. The Training Materials state that

> [t]he specification also contemplates but **does not exemplify** variants of the protein wherein the variant can have any or all of the following:

> substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Id. (emphasis added).

The close analogy between the instant case and Example 14 of the Training Materials is hard to miss. Claims 40 and 45 describe the claimed genus in structural (80% or 90% sequence identity, respectively) and functional (binding activity) terms that are nearly identical to those of Example 14. Appellants highlight only two important points in this regard. First, like the specification in Example 14, Appellants' Specification states that methods for creation of protein variants are well-known in the art. Specification, p. 29, lines 6-8. Appellants' specification goes far beyond such minimal disclosure, however, by providing various methods for creating variants of the species described in the disclosure as well as methods for determining interaction between two peptides. See generally Specification, p. 30-35; id. at p. 28, lines 13-21.

Second, Examiner failed in the Final Rejection to so much as respond to Appellants' well-reasoned discussion of Example 14, in spite of explicit instructions in the MPEP that examiners should, in any repeated rejection, "take note of the applicant's argument and answer the substance of it." MPEP § 707.07(f), 8th Edition, Rev. 3, Aug. 2005, p. 700-123 (emphasis added). Examiner did not attempt to distinguish Example 14 because no meaningful distinction exists. The only difference between Example 14 and the present claims is that the present invention involves proteins whose function is one of binding rather than catalyzing a particular reaction. This is, however, a difference without a distinction because binding activity is just as much a "function" as enzymatic activity.

In sum, Appellants' Specification has more than complied with both the binding Federal Circuit case law and the PTO's guidelines regarding the § 112, first paragraph, written description requirement.

C. Rejection under 35 USC § 112 – Enablement

Claims 40-50 stand finally rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking a disclosure that enables the full scope of the claims. Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention without undue experimentation. Ratheon Co. v. Roper Corp., 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Enablement is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive. Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1540, 1555, 220 USPQ 303, 315 (Fed. Cir. 1983). In order to establish a prima facie case of lack of enablement, an examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Federal Circuit has provided several factors to aid in the determination of whether a claimed invention is enabled by a patent specification or requires undue experimentation. In re Wands, 858 F.2d 731 (Fed. Cir. 1988). The Wands factors include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability or the art, and (8) the breadth of the claims. Id. at 737.

1. No Prima Facie Case

In an attempt to establish a prima facie case of nonenablement, Examiner alleges that the only way for one of skill in the art to practice the full scope of the invention is either to produce and test every possible permutation and pairing or to predict which permutations and pairings will result in a viable complex. Examiner further alleges that the specification gives no guidance as to which variants would retain binding activity, from which Examiner concludes that predicting which variants will interact "would require a level of ingenuity beyond what is expected from on [sic] of ordinary skill in the field." Final Rejection, p. 11, 1st paragraph. Finally and most importantly, Examiner admits that one of ordinary skill in the art could "produce all of these [variants] with art

known techniques," Final Rejection, p. 11, 1st paragraph, but then alleges without proof that such activities would be "burdensome."

Because the experimentation needed to practice the claimed invention is routine and not undue, Appellants respectfully assert that Examiner has failed to establish a prima facie case of nonenablement. In order to produce one protein complex in accordance with the present invention, an artisan need simply produce a survivin and/or HDLC1 variant and test its ability to interact with a corresponding variant. See Specification, p. 29, lines 6-14; id. at pp. 118-119, Example 1. Sometimes the variants chosen by the artisan will not result in a viable complex, but potentially inoperable embodiments are neither encompassed by the claims nor would they constitute per se evidence of nonenablement if they were encompassed. MPEP § 2164.08(b), 8th Edition, Rev. 3, Aug. 2005, p. 2100-207. While it is true that producing every possible variant or predicting viable interacting variants are ways to practice the invention, the trial-and-error method outlined above is clearly a reasonable alternative that would not involve undue experimentation.

Further, Appellants have given **ample** guidance in designing peptide variants that would fall within the functional limitations of the claims. The specification clearly designates the likely binding regions of both survivin and HDLC1. Specification, p. 29, lines 6-14; see also p. 21, Table 1; p. 23, lines 25-31. For example, in Table 1, Applicants have shown that survivin fragments including amino acid residues 89-143, or 3-99 or 47-143 are capable of interacting with HDLC1. Specification, p. 21, Table 1. The Specification explicitly instructs artisans to replicate these regions when designing fragments that will likely retain binding ability. Specification, p. 29, lines 6-14. One of skill in the art would clearly see this region as one where mutations are more likely to abolish binding. One of skill in the art would also clearly recognize that deletions, substitutions and insertions of amino acid residues outside this region of survivin would probably not affect its binding activity to HDLC1. Hence, contrary to Examiner's allegations, the guidance in the disclosure enables one ordinarily skilled in the art to predict which amino acids could be mutated while preserving binding activity.

The Examiner relies on U.S. Patent 6,168,926 to support the position that those skilled in the art recognize that high sequence identity cannot be used as a sole standard

for enablement. As previously discussed, the present invention does not rely solely on high sequence identity to enable the present claims, but further on a functional requirement that the proteins to interact. Applicants assert that the present invention is enabled by these requirements coupled with sufficient guidance on determining functional activity. Furthermore, Applicants believe that the patent relied upon by the Examiner actually supports enablement of the present invention by showing that survivin homologues can be readily made and are known in the art.

Finally and most importantly, Examiner equates a large quantity of experimentation with "undue experimentation." In so doing, Examiner has in essence turned the eight-factor Wands test into a one-factor test where quantity of experimentation demonstrates the undue nature of experimentation. Properly applied, the Wands test is more qualitative than quantitative because it focuses on the type of experimentation that is required to practice the invention. Wands, 858 F.2d at 737; MPEP § 2164.06, 8th Edition, Rev. 2, May 2004, p. 2100-200. Creating variants of a well-known peptide is routine to the point of bordering on the mundane. See generally Specification, p. 30-35 (describing several art-known techniques and citing to several art sources). Testing for a protein interaction between two known peptides is similarly unremarkable. Specification, p. 42-50. Skilled artisans have numerous proven methods at their disposal for each activity. In light of the guidance provided in the Specification regarding binding regions for survivin and HDLC1, even the quantity of experimentation is not all that great. In sum, Examiner has failed to provide any evidence or reasoning tending to show that the experimentation an artisan would have to undergo would be undue.

2. Sufficient Enablement

Though not binding precedent, the Board of Patent Appeals decisions shed light on the enablement of Appellants' disclosure and do not support Examiner's position. Ex parte Yuejin Sun, for example, presents a strikingly analogous factual situation to the present case. Appeal No. 2003-1993, Application No. 09/470,526 (BPAI 2004). The patent at issue in Sun claimed polynucleotide sequences 80% identical to the native coding region. The Board found such claims enabled because the patent disclosed

sufficient means for testing the activity of the resulting polypeptide. A very similar claim was allowed in Ex parte Rachel Meyers. Appeal No. 2003-1820, Application No. 09/464,039 (BPAI 2004). In Meyers the Board stated "the claims are limited to nucleotide sequences meeting both the structural requirements of these claims and the claimed functional requirement," and also noted that the skilled artisan would be able to construct polynucleotides that retained the claimed catalytic function.

The similarities between the present case and Sun and Meyers are clear, but Appellants point out one helpful distinction between them. The claims in Sun and Meyers were directed to a polynucleotide and the Board found enablement in instructions for the testing of the function of the resulting polypeptide. In other words, Sun and Meyers presented an additional degree of experimental separation between the claimed variants and the claimed, experimentally verifiable function – i.e. transcription of the polynucleotide into a viable polypeptide. Under Examiner's quantitative analysis, artisans would need to predict protein activity despite one additional layer of potential unpredictability. Conversely, Appellants have enabled artisans more than that found sufficient in both Sun and Meyers by providing and claiming well-known polypeptides and their interaction.

That there are numerous or even "infinite possible choices," Final Rejection, p. 12, 1st paragraph, in practicing a genus claim does not preclude a finding of enablement. The United States Supreme Court has ruled that "the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject matter." Minerals Separation v. Hyde, 242 U.S. 261, 271 (1916) (emphasis added). At issue in Minerals Separation was a process for separating metallic minerals from crude ore. Defendants contended that the patent was invalid for lack of enablement because "[t]he composition of ores varie[d] infinitely, each one presenting its special problem, and [the patent did not specify] the precise treatment which would be most successful... in each case." Id. The Court found such "infinite" variation unproblematic because it would not have been reasonable to require the patentee to list every possible permutation of the invention's variables. Id. Most importantly, the Court stated that "[t]he process is one for dealing with a large class of substances and the range of treatment within the terms of the claims,

while leaving something to the skill of persons applying the invention, is clearly sufficiently definite to guide those skilled in the art to its successful application." Id.

The present Specification, like that at issue in Minerals Separation, is sufficiently enabling to guide those skilled in the art to successful application of the invention because it discloses (1) the prototype of each interacting member, Specification, p. 21, Table 1, (2) ample instructions on engineering every possible variant thereof, id. at p. 30-35, and (3) several different methods of testing for an interaction, id. at p. 42-50. Even if, as Examiner alleges, the universe of permutations were indeed infinite and it would be prohibitively burdensome for one of ordinary skill in the art to synthesize and test them all, this fact would actually weigh in favor of a finding of enablement under Minerals Separation. It would be "obviously impossible to specify in a patent" these infinite variations. Minerals Separation, 242 U.S. at 271. The present Specification has, by defining the genus in terms of structure and function and by providing several working examples, included at least the reasonable level of certainty required under Mineral Separations. Id.

Appellants therefore respectfully request that Examiner's enablement rejection under § 112, first paragraph, be reversed and claims 40-50 be allowed.

D. Conclusion

Appellants respectfully request that the rejection of claims 40-50 under 35 USC § 112, first paragraph for allegedly reciting new matter, being based on an insufficient written description, and being based on a nonenabling disclosure be reversed.

The Director is hereby authorized to charge the required Appeal Brief filing fee of $250.00, for a small entity, as set forth in 37 C.F.R. § 41.20(b)(2), or to credit any overpayment to Deposit Account No. **50-1627**. A petition for a one-month extension of time is being filed concurrently with this response. Provisions for the payment of the necessary fee for this extension of time have been made in the petition. Therefore, it is believed that no other extension of time, nor any additional fees, are due with this brief. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency, or credit any overpayment, to Deposit Account no. **50-1627**.

Respectfully submitted,

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(8) CLAIMS APPENDIX

Claim 40 (previously presented): An isolated protein complex comprising a first protein interacting with a second protein, wherein

said first protein is selected from the group consisting of:

(a) survivin, or a fragment thereof that interacts with HDLC1;

(b) a first polypeptide having an amino acid sequence at least 80% identical to that of (a), and that interacts with HDLC1; and

(c) a first fusion protein comprising (a) or (b); and

wherein said second protein is selected from the group consisting of:

(i) HDLC1, or a fragment thereof that interacts with survivin;

(ii) a second polypeptide having an amino acid sequence at least 80% identical to that of (i), and that interacts with survivin; and

(iii) a second fusion protein comprising (i) or (ii).

Claim 41 (previously presented): The isolated protein complex of Claim 40, wherein said first protein is survivin.

Claim 42 (previously presented): The isolated protein complex of Claim 40, wherein said first protein is said first fusion protein.

Claim 43 (previously presented): The isolated protein complex of Claim 40, wherein said fragment of survivin comprises amino acid residues 89 to 142, 3 to 99, 47 to 142, or 47 to 99 of survivin.

Claim 44 (previously presented): The isolated protein complex of Claim 40, wherein said first protein is covalently linked to said second protein.

Claim 45 (previously presented): An isolated protein complex comprising a first protein interacting with a second protein, wherein

said first protein is a first fusion protein comprising a first detectable tag and

(a) survivin;

(b) a survivin fragment containing a contiguous span of 10 amino acid residues of survivin, and that interacts with HDLC1; or

(c) a first polypeptide having an amino acid sequence at least 90% identical to that of (a), and that interacts with HDLC1; and

wherein

said second protein is a second fusion protein comprising a second detectable tag and

(i) HDLC1;

(ii) an HDLC1 fragment comprising a contiguous span of 10 amino acid residues of HDLC1, and that interacts with survivin; or

(iii) a second polypeptide having an amino acid sequence at least 90% identical to that of (i), and that interacts with survivin.

Claim 46 (previously presented): The protein complex of Claim 45, wherein said first protein is said first fusion protein comprising said first detectable tag and survivin; and said second protein is said second fusion protein comprising said second detectable tag and HDLC1.

Claim 47 (previously presented): The isolated protein complex of Claim 40, wherein said second protein is HDLC1.

Claim 48 (previously presented): The isolated protein complex of Claim 40, wherein said second protein is said second fusion protein.

Claim 49 (previously presented): The isolated protein complex of Claim 40, wherein said first protein comprises an amino acid sequence that is at least 80% identical to that of amino acid residues 89-142, 3-99, 47-142 or 47-99 of survivin.

Claim 50 (previously presented): The isolated protein complex of Claim 40, wherein said first protein comprises an amino acid sequence that is at least 90% identical to that of amino acid residues 89-142, 3-99, 47-142 or 47-99 of survivin.

(9) EVIDENCE APPENDIX

CONTENTS

EXHIBIT 1:

Example 14 ("Product by Function"), *USPTO Revised Interim Written Description Guidelines Training Materials,* pages 53 through 55.

(10) RELATED PROCEEDINGS APPENDIX

None

Exhibit 1

Example 14: Product by Function

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of **A** $\longrightarrow$ **B.** The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A $\longrightarrow$ B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that

applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.